Sound Sleep – clearly a matter of the heart

Combined therapy of Cheyne-Stokes respiration and Obstructive Sleep Apnea

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homecare

SOMNO*vent* CR

A product monograph with usage tips

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Dr. Martina Bögel

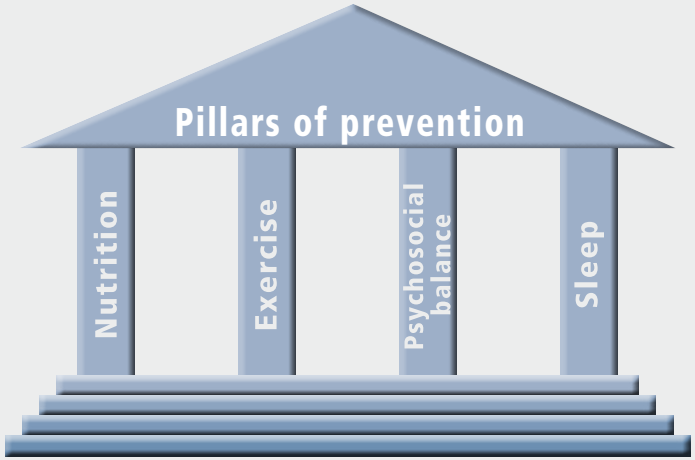
Hamburg, 7 July 2008

Foreword

Sleep-related breathing disorders are among the medical challenges of modern society. Like cardiovascular diseases, they develop from hypertension, diabetes and lipometabolic disorders. An important risk factor shared by both sleep-related breathing disorders and cardiovascular diseases is overweight, a problem faced by an increasing proportion of society due to bad nutritional habits and lack of exercise. Current studies show that poor or inadequate sleep can affect metabolism in such a way that weight gain is encouraged.

Prevention of cardiovascular disease is supported by the three pillars of nutrition, exercise and psychosocial balance. An urgently needed fourth pillar – sleep – should be added to make preventive measures even more effective. For patients who are already affected by a serious illness such as heart failure, physicians should determine whether nighttime breathing disorders are also present. If left untreated, they could have a negative effect on the patient's prognosis.

This product monograph is intended to share knowledge about the significance of sleep-related breathing disorders in patients with heart failure and to inform the reader of current therapeutic applications with special consideration given to the use of the SOMNO*vent* CR therapy device for this patient group.



1. SOMNO*vent* CR at a glance

Use

- SOMNO*vent* CR is a ventilator which provides automatically regulated pressure positive ventilation to patients with central sleep apnea syndrome accompanied by Cheyne-Stokes respiration and delivers combined treatment of co-prevalent obstructive sleep apnea syndrome and complex sleep apnea.

Principle

- Ventilation therapy with SOMNO*vent* CR is anticyclical modulated ventilation (also known as adaptive servo-ventilation) which continuously adjusts respiratory support to the needs of each patient.
- CR mode combines the advantages of intelligent reaction to central events, including those related to periodic breathing, with automatic regulation in response to obstructive events (similar to auto-CPAP therapy).

Details

Functional components of automatic-regulation:

- Variation in delivery of breath/pressure support based on continuous anticyclical modulation of delta-I-E (difference IPAP-EPAP) to periodic breathing pattern.
- Decrease in EPAP improves patient comfort with pressure relief softPAP.
- Pressure regulation of EEPAP efficiently eliminates obstructive events.
- Use of backup minimum breath rate in the event of apnea.

Process

Process optimization:

- With very few setting parameters: plug and breathe
- Menu-based operation guarantees simplified device set-up by doctor
- Data on therapy effectiveness available at a glance on PC and in device software.
- Simple operation is convenient for doctor and provider. Gentle breathing regulation and low operating noise level make the patient more comfortable.

Ill.1
SOMNO*vent* CR – for patients with Cheyne-Stokes respiration combined with obstructive sleep apnea

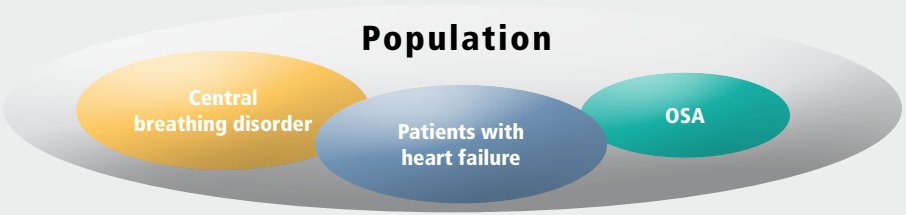
2. Introduction

Obstructive Sleep Apnea (OSA) syndrome was first reported some 30 years ago (57). Awareness of the problem remained low until data regarding its prevalence were published (58). It is assumed that approximately 2 % of women and 4 % of men are affected by OSA (56), with the highest prevalence occurring between 35 and 60 years of age.

The discovery of Cheyne-Stokes respiration (CSR) as a central disorder of respiratory regulation was made even earlier. It was first reported in 1818 by Dr. John Cheyne (9) and in 1854 by Dr. William Stokes (10). Even at that time periodic breathing was known to be causally related to heart disease and patients' prognosis was poor.

A central respiratory regulation disorder with underlying heart failure is not a rare disease. Approximately 1 to 1.5 % of the general population suffer from chronic heart failure (1). In later life (> 50 years) prevalence increases significantly. More than 50 % of patients with heart failure in NYHA (New York Heart Association) classes II to IV are also affected by a sleep-related breathing disorder (SRBD). About 30 to 40 % of affected patients indicate a central Cheyne-Stokes type (2, 3, 4) of breathing disorder. A current study involving patients in NYHA classes II to III and with an ejection fraction of < 40 %, showed that 71 % of the patients had an AHI (apnea-hypopnea index) of > 10/hr, with 43 % affected by OSA and 28 % by CSR (68).

Sleep-related breathing disorders Prevalence and comorbidity



Ill. 2
It is estimated that more than 90 % of patients with heart failure also have a sleep-related breathing disorder that has not yet been diagnosed. Because such a disorder, whether obstructive and/or central, represents an additional cardiovascular risk, those affected should be diagnosed and treated. Sleep-related breathing disorders also appear during the post-acute phase in 40 to 60 % of stroke patients.

3. Definition of syndromes

According to ICSD-2 (54, the international classification of sleep disorders), central sleep apnea with Cheyne-Stokes respiration and obstructive sleep apnea are defined as follows:

Central sleep apnea with Cheyne-Stokes respiration

- Polysomnography: ≥ 10 central apneas/hr with a crescendo-decrescendo pattern of breathing associated with frequently occurring waking reactions and altered sleep structure
- Association with severe internal/neurological disease (heart failure, kidney failure, apoplexy)
- Facultative: excessive daytime sleepiness, complaints of insomnia, nighttime waking with respiratory distress
- Diseases not more effectively explained by other sleep disorders or medication misuse/drug abuse

The typical CSR patient

- has heart failure (generally NYHA II to IV)
- is male
- has hypocapnia with $PaCO_2$ < 38 mmHg
- is more than 60 years old
- shows signs of atrial fibrillation (36)

Obstructive sleep apnea, adults

Required: A, B and D or C and D

A

Medical history (at least one of the following criteria)

1. Unintentionally falling asleep during normal wake phases, daytime sleepiness, non-recuperative sleep or insomnia
2. Nighttime waking with apnea, choking fits, gasping for breath
3. Bed partner observes loud snoring or apnea while patient is sleeping

B

- Polysomnography: ≥ 5 respiratory events/hr (apnea, hypopnea, respiratory effort-related arousal or RERAS) with respiratory effort during each respiratory event

or

C

- Polysomnography: ≥ 15 respiratory events/hr (apnea, hypopnea, respiratory effort-related arousal or RERAS) with respiratory effort during each respiratory event

D

- Diseases not more effectively explained by other sleep disorders, an internal or neurological disease, medication misuse/drug abuse

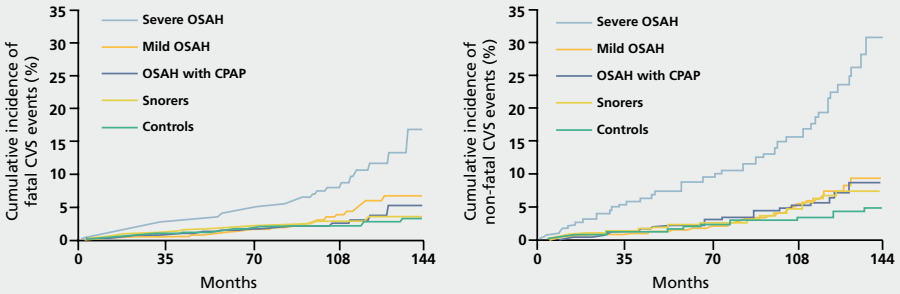
4. Sleep-related breathing disorders and cardiovascular risk – Heart disease and sleep-related breathing disorders

It has been documented that sleep-related breathing disorders represent a risk to the cardiovascular system (5). Furthermore, the presence of OSA increases the risk of severe cardiac events (59).

A number of pathological changes associated with OSA also occur during the early stages of heart failure. They include:

- Increased sympathetic activity (60)
- Increased level of catecholamine in plasma and urine (60)
- Suppressed level of nitric oxide in vasoactive endothelins (61)

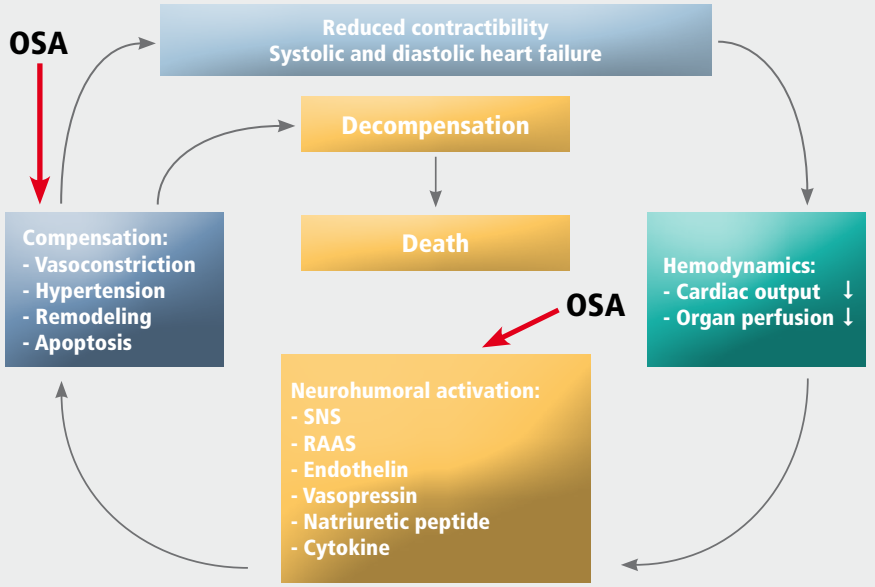
The team of Marin et al. was able to show that patients with OSA have a higher risk of cardiac events. That risk can be significantly reduced by CPAP therapy (cf. Ill. 3).



Ill. 3
Source: Marin, Lancet: 2005*.
The graphs show the development of fatal and non-fatal cardiovascular events over a period of 144 months in the groups of healthy subjects (controls), snorers, subjects with mild OSAH (AHI 5-15), moderately severe OSAH (AHI 16-30) and severe OSAH (AHI > 30) and OSAH patients treated with CPAP. The conclusion based on these results is that untreated OSAH patients (AHI > 30) show a threefold higher risk of fatal and non-fatal events. Snorers face no additional cardiac risk.

* Courtesy of "The Lancet"

In OSA and in heart failure patients similar mechanisms of neurohumoral activation and compensation take hold which may progress in the presence of both types of morbidity. The following illustration shows the vicious circle of heart failure and the pathological "overlay" of obstructive sleep apnea.



Ill. 4
Vicious circle of heart failure
Arrows mark the areas in which identical pathological mechanisms are "triggered" in OSA cases.

What is the situation in cases of central respiratory regulation accompanied by severe heart failure?

More importance has been attached in recent years to the use of devices for non-invasive positive-pressure ventilation for the treatment of sleep apnea syndrome with heart failure which does not respond to medication. Data provide evidence that patients with heart failure and Cheyne-Stokes respiration have a poorer prognosis than heart failure patients without central respiratory regulation disorders (7). Studies in which non-invasive positive pressure ventilation (CPAP) was used as supplemental therapy show that this type of treatment reduces morbidity and mortality (8).

5. Description, diagnosis and definition of central, mixed and obstructive events and complex sleep apnea

Central apnea is defined as a lack of (nasal/oral) air flow due to the absence of respiratory stimulus (6).

Hypopnea* is said to be present when

1. a decrease is seen in respiratory amplitude > 50 % compared to normal breathing during sleep. The base amplitude of normal breathing is equal to mean amplitude under normal breathing during sleep or, if stable breathing is not present, to the mean amplitude of the three largest tidal volumes within the two minutes prior to the respiratory event or
2. a significant decrease in respiratory amplitude during sleep which does not reach the 50 % limit, but which is accompanied by desaturation of > 3 % or an arousal (6).

In the absence of central respiratory activity, any effort in respiratory muscles must be ruled out, as that would point to an obstructive event. Today's diagnostic standard is still the esophageal probe, which is used primarily for research purposes since it is an invasive method that does not appear to be suitable for routine use. In routine clinical use, nasal air flow is combined with output from sensors for thoracic and abdominal movement to distinguish between central events and obstructive events.

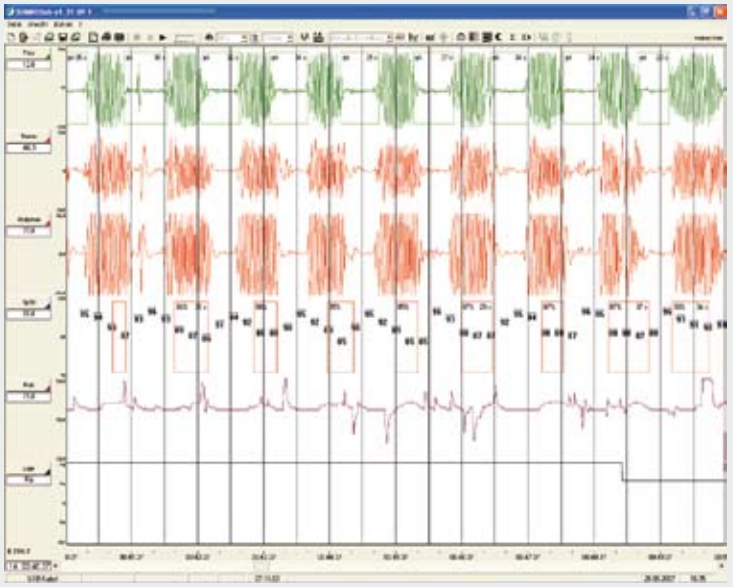
Cheyne-Stokes respiration is present when a typical crescendo-decrescendo respiratory pattern is reflected in the polysomonograph curves of nasal flow and thoracic and abdominal movements.

Illustration 5 shows the typical breathing pattern of Cheyne-Stokes respiration.

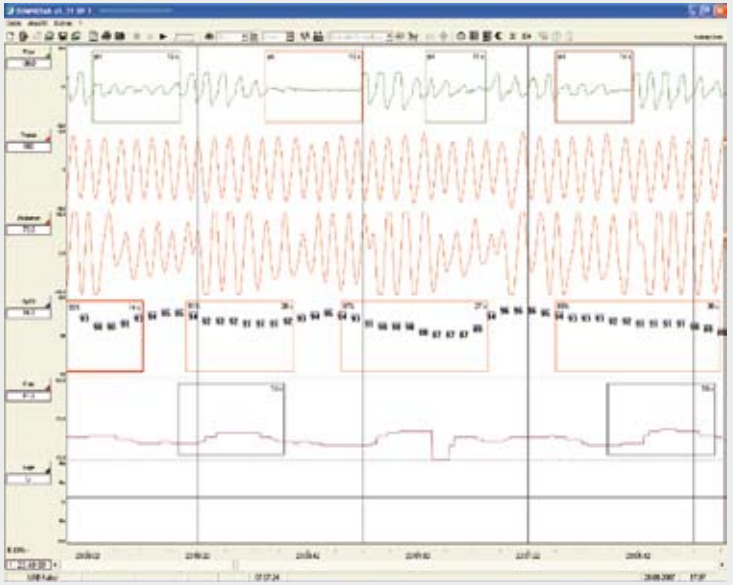
A **mixed form of apnea** is indicated by an obstructive event that follows an initial brief loss of central respiratory stimulus. Mixed apnea is classified as a type of obstructive sleep apnea.

Obstructive events (Ill. 6) are defined as recurring partial or complete restrictions (flattening, hypopnea) in air flow of ≥ 10 seconds during sleep despite continued respiratory effort.

* Event definitions are based on the AASM guidelines of 1999.



Ill. 5
Patient with Cheyne-Stokes respiration. It is easy to see the crescendo-decrescendo pattern of breathing. Polysomnographic recording with SOMNO*lab*.



Ill. 6
Patient with obstructive sleep apnea. Polysomnographic recording with SOMNO*lab*.

Whether the disorder known as "complex sleep apnea" is a unique clinical syndrome is the subject of current discussions (66). It has been observed in some OSA patients that obstructive events disappear under CPAP therapy, only to be replaced by central events and/or Cheyne-Stokes respiration (67). Often these patients also suffer from heart failure. However, a number of other possible causes have been identified, including hyperventilation brought on by CPAP therapy. In such cases it is recommended that the patient's $PaCO_2$ be checked. Regardless of the cause, the therapeutic goal should be to reduce the patient's hypocapnia or hyperventilation (see Therapeutic approaches). The appearance of complex sleep apnea under CPAP therapy can be a clear indication for the use of anticyclical modulated ventilation (ACMV), which efficiently eliminates central events.

Prior to the use of ACMV, it is critical that a differential diagnosis be made and the lung and circulatory functions be examined.

Other possible causes of the "phenomenon" of complex sleep apnea (in order of declining likelihood) are:

- Non-compensated nose/mouth leakage
- Hyperventilation caused by CPAP/ bilevel therapy
- Over-titration by CPAP
- Less than ideal in/ex pressures in bilevel therapy
- Heart failure
- Chronic obstruction of lower airways (e.g., residual volume, intrathoracic gas volume, elevated airway resistance)
- Restriction (reduced total lung capacity)
- Sleep status, body position
- Hering-Breuer reflex
- Glottic closure reflex

Heart failure patients with SRBD frequently show a leading symptom of a central respiratory regulation disorder with normocapnia, possibly combined with obstructive sleep apnea or complex sleep apnea.

*Source: Presentation on differential diagnostic clarification by Dr. Raschke/Norderney, SNAK Meeting Hamburg 200

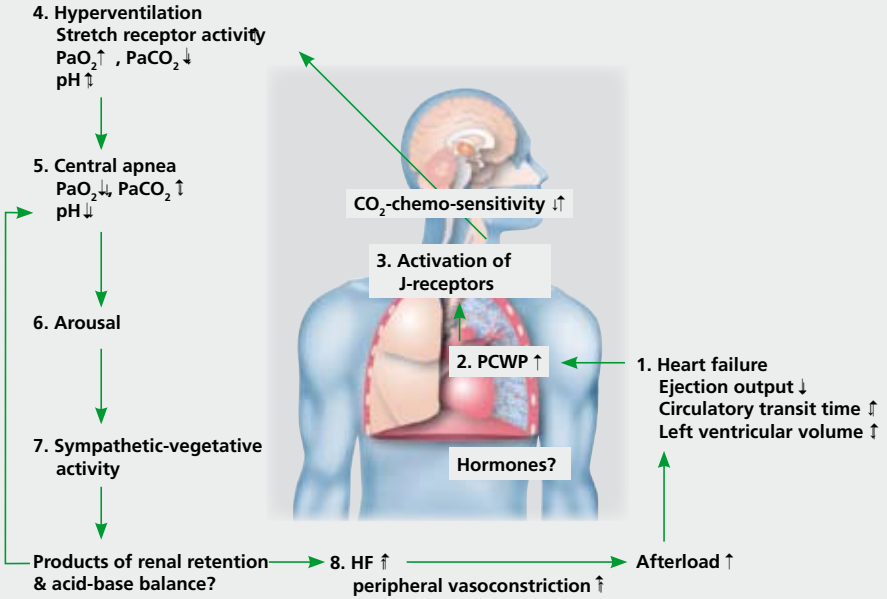
6. Physiology and pathophysiology of respiratory regulation

Central apnea is triggered by a disorder in the respiratory control center. In cases of Cheyne-Stokes respiration with internal or neurological origins, a higher CO_2 response has been observed. Human respiratory regulation is managed centrally by chemo-sensitive structures in the brain stem, the medulla oblongata, which reacts to changes in $PaCO_2$ and pH, and by peripheral chemoreceptors, the carotid body (glomus caroticum) and aortic bodies (glomera aortica). The bodies forward the information about PaO_2 and $PaCO_2$ to the respiratory center in the medulla oblongata. The central chemoreceptors generally take two to five minutes to react to changes in $PaCO_2$ (12). The respiratory cycle in Cheyne-Stokes respiration is composed of crescendo-decrescendo ventilation and apnea. Because the cycle lasts less than two minutes, the central chemoreceptors do not receive sufficient stimulation. One theory holds that peripheral chemoreceptors are responsible in part for the onset and continuation of Cheyne-Stokes respiration. Support for that theory is the rapid kinetic with which an external feed of CO_2 can eliminate central apnea. Current studies indicate that the peripheral chemoreceptors are hypersensitive in their reaction to CO_2 (13, 14). Healthy subjects react to a rise in CO_2 or a reduction in pH with an increase in ventilation, while a reduction in CO_2 or an increase in pH trigger a reduction in ventilation. Patients with Cheyne-Stokes respiration undershoot the apnea threshold and react accordingly with the familiar pattern of crescendo-decrescendo breathing and central apnea. The apnea threshold, which is influenced by hormones, differs among healthy subjects too. Testosterone is said to be responsible for the more pronounced respiratory instability in men (15, 16).

During the transition from a waking state to non-REM sleep, there is normally a reduced sensitivity to CO_2 and O_2, which is associated with an increase in $PaCO_2$ of 3 to 7 mmHg and a reduction of PaO_2 of 3.5 to 9.4 mmHg (17, 18). During REM sleep the CO_2 response is further reduced (19, 20, 21). An increased CO_2 response has been observed in patients with normocapnia/hypocapnia apnea even when they are at rest. A rise in $PaCO_2$ or a decrease in CO_2 sensitivity does not occur during sleep (22, 23). Ventilation normalizes only during deep sleep stages and REM sleep; Cheyne-Stokes respira-

tion therefore occurs primarily in NREM 1 + 2. As with obstructive respiratory events, central apnea and Cheyne-Stokes respiration can lead to arousals and consequently to sleep fragmentation. It is not yet known whether the arousals develop due to oxygen saturation, that is, a chemical activation, or as a result of the increased tidal volumes and stimulation of stretch receptors during hyperventilation. Some support for the latter theory is the fact that arousals frequently occur after ventilation has begun. Increased sympathetic activity and elevated levels of catecholamine have been measured in patients with Cheyne-Stokes respiration (24, 25). The following is a model of the pathogenesis of Cheyne-Stokes respiration with heart failure (Ill. 7).

Pathogenesis of Cheyne-Stokes respiration with heart failure



Ill. 7
Model of pathogenesis of Cheyne-Stokes respiration with heart failure

7. Pathophysiology of Cheyne-Stokes respiration with heart failure

Patients with heart failure have a diminished cardiac ejection fraction, prolonged blood transit time and/or increased left ventricular volume. It is frequently observed that these patients have a heightened activation of the sympathetic nervous system with an increased release of catecholamine. The diminished cardiac ejection fraction prompts an increase in pulmonary capillary wedge pressure (PCWP), which activates the J-receptors and triggers hyperventilation by stimulating the vagus nerve. An increase in tidal volume can trigger arousals via the vagus nerve cord. Hyperventilation in turn leads to a reduction in $PaCO_2$ or to a renewed increase in pH. Central apnea results if the $PaCO_2$ level remains below the apnea threshold or if chemical stimulation of the respiratory center does not occur due to a lack of alkalosis. During apnea the $PaCO_2$ rises and PaO_2 sinks. The resulting lowered pH causes an increase in ventilation and resumption of periodic breathing with alternating phases of apnea and hyperventilation.

A drop in oxygen saturation leads to a deterioration in the supply of oxygen to the myocardium. At the same time desaturation and/or an increase in $PaCO_2$ activates the sympathetic nervous system. This situation increases – by means of quickened heart rate – the need for more oxygen. In addition, peripheral vasoconstriction increases and with it afterload, which further burdens the heart and reduces the ejection fraction. Clarification has not yet been offered for the etiology of the elevated CO_2 chemo-sensitivity. It is surmised that hormones, particularly testosterone, could play a role. Furthermore, data are not available regarding the influence of the renal acid-base balance or renal insufficiency on Cheyne-Stokes respiration.

Pathogenesis

Cheyne-Stokes respiration is based on instability in central respiratory regulation. The following factors are primarily responsible for periodic breathing of cardiac origin:

- Limited cardiac function with elevated ventricular volume and prolonged blood transit time
- Hypocapnia with increased CO_2 sensitivity
- Tendency toward arousals with sleep fragmentation

Cardiac dysfunction

The prerequisite for a diagnosis of Cheyne-Stokes respiration is a central neurological disorder (idiopathic or acquired, such as apoplexy) or previously identified heart failure. A satisfactory explanation has not yet been offered for the occurrence of hypocapnia with periodic breathing in heart failure patients. However, in a 1956 study involving dogs, a delay system in the transit time of blood from the lungs to the brain induced Cheyne-Stokes respiration (26). The occurrence of Cheyne-Stokes respiration is more frequent in patients with ischemic cardiomyopathy than with heart failure of other causes.

Hypocapnia

Patients with reduced myocardial ejection fraction have a lowered $PaCO_2$ at rest and during sleep. Hypocapnia does not appear to be directly related to the heart's ejection fraction (27, 28, 29). Because $PaCO_2$ does not increase during sleep, there is a reduced difference between basal $PaCO_2$ and the CO_2 apnea threshold (30). The cause of hypocapnia is increased chemo-sensitivity. Both the central and peripheral chemo-receptors appear to be altered (31, 13, 32). An increased PCWP correlates to hypocapnia as well as to severe Cheyne-Stokes respiration (33, 34). It is possible that the vagal afferents are stimulated by intrapulmonary juxtacapillary receptors (35). These connections, however, do not explain the significantly higher proportion of male patients with Cheyne-Stokes respiration (36; risk factor 3, 50). A connection between testosterone and the apneic threshold has been documented (15). No examination has been made of how renal function affects Cheyne-Stokes respiration; it is conceivable that renal pH regulation has an effect on periodic breathing.

Hypoxemia

In contrast to what is known about the role of obstructive sleep apnea in Cheyne-Stokes respiration, the significance of desaturation and hypoxemia is much less certain. The influence, however, on the development of closely associated central sleep apnea and periodic breathing has been documented (37). It is quite likely that another mechanism is responsible. Patients with manifest heart failure and Cheyne-Stokes respiration, on the other hand, show generally normal oxemic blood gas levels at rest and a normal respiratory response to hypoxemic stimuli (32).

When desaturation occurs in a sleeping patient, the temporal connection between oxygen desaturation and post-apneic hyperventilation is not as obvious as it is in obstructive sleep apnea. An arousal in this case is frequently observed first at maximum hyperventilation and not immediately after apnea. Still to be examined are the questions about which vegetative "stress factor" acts on those patients who are affected by Cheyne-Stokes respiration accompanied by manifest heart failure and by obstructive sleep apnea; how pathological mechanisms possibly interact; and what potentially negative effect they have on the cardiovascular system.

Contrary to earlier statements, it appears that Cheyne-Stokes respiration may be treated to a certain extent with oxygen inhalation (38, 39). It should be kept in mind, however, that the effect of the oxygen, according to the available data, can be attributed to a CO_2 increase prompted by supplemental oxygen and not to improved oxygen saturation (40, 41).

Arousals with sleep fragmentation

Even for healthy persons the transition from waking to sleeping is a period of respiratory instability. As the threshold at which hypocapnia can induce apnea is very close to basal $PaCO_2$, an increase in ventilation such as a sigh or an arousal suffices to induce a central apnea. This phenomenon has been observed in healthy subjects. Basal $PaCO_2$ increases as deeper sleep stages are reached, allowing breathing to stabilize because the greater delta $PaCO_2$ makes it more difficult to reach the apnea threshold.

Since a rise in basal $PaCO_2$ does not occur during sleep in patients with Cheyne-Stokes respiration, the tendency toward unstable breathing is significantly greater. Exacerbating the situation further, patients hardly ever reach the deep and REM sleep stages due to sleep fragmentation. Moreover, consecutive episodes of hyperventilation accompanied by a reduction in $PaCO_2$ lead to even more respiratory instability.

Given the frequent coexistence of the disorders, pathological events of Cheyne-Stokes respiration interact with those of obstructive respiratory events. Currently one can only surmise the additional burden this comorbidity places on the cardiovascular system.

8. Clinical manifestation of Cheyne-Stokes respiration

Although the number and frequency of respiratory events are the same as in OSA, the daytime symptoms in patients with Cheyne-Stokes respiration are not as pronounced. Some doctors attribute this to the patients' differing life situations. OSA patients are 10 years younger on average than patients with heart failure and most still work fulltime. Daytime naps may be responsible for the less pronounced daytime sleepiness in heart failure patients.

The literature lists the following symptoms in patients with Cheyne-Stokes respiration (24, 42, 43):

- Daytime sleepiness
- Oscillating blood pressure/cardiac rate (also possible in waking state)
- Activation of neuroendocrine systems (elevated catecholamine level)
- Altered cardiac rate variations (as indicator of reduced vagal tone)
- Reduced arterial $PaCO_2$
- Elevated CO_2 chemo-sensitivity (increased hypercapnic respiratory response)

Sleep parameters:

- Increased stage 1 sleep
- Reduced deep sleep (Slow-Wave Sleep)
- Decreased REM sleep
- Frequent arousals
- Sleep fragmentation
- Shortened sleep onset latency

The following indications of CSR should be considered:

- Apparent apnea
- Paroxysmal Nocturnal Dyspnea (PND)
- Masked daytime sleepiness

Note!

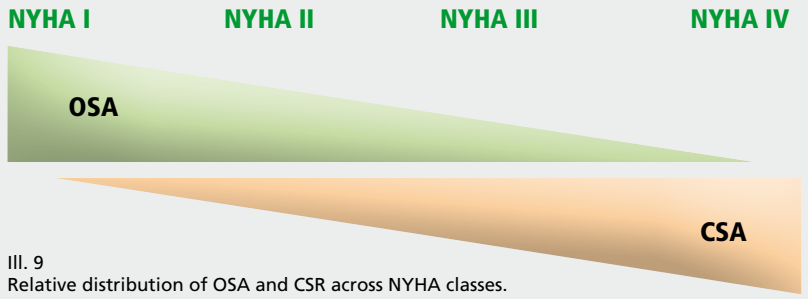
The Epworth Sleepiness Scale (ESS) has not been validated for chronic heart failure patients with Cheyne-Stokes respiration. How can heart failure patients with absolute obstructive sleep apnea be distinguished from those who have an almost absolute central respiratory regulation disorder with a Cheyne-Stokes pattern? The following pages contain some patient descriptions and reports of professional observations.

Predominantly absolute OSA	Predominantly absolute CSR
LVEF tends not to be reduced	LVEF < 35 %
Normocapnic	Hypocapnic: $PaCO_2$ < 38 mmHg
Snoring	Little or no snoring
Overweight	Initially normal weight, later overweight

Patients with heart failure – typified with regard to sleep-related breathing disorders

Note!

In patients with severe heart failure, effective treatment of OSA can unmask CSR. Experience shows that the more advanced heart failure is, the more likely it is that the patient will suffer from Cheyne-Stokes respiration and the less likely it is that obstructive sleep apnea will emerge. As the disease progresses, the patient loses weight (primarily NYHA IV) and effectively reduces one of the main risk factors for OSA. This observation has not yet been confirmed by a study. This tendency is depicted in the following illustration.



Ill. 9
Relative distribution of OSA and CSR across NYHA classes.

It can be assumed that a relatively large number of heart failure patients are diagnosed, according to ICSD-2, with CSR and co-prevalent OSA. Detailed investigations of this matter have yet to be made.

9. Therapeutic approaches

Drug treatment should first be used on patients with Cheyne-Stokes respiration. In recent years the therapeutic effectiveness of beta blockers has been improved, resulting in better treatment of heart failure and a subsequent delay in the onset of Cheyne-Stokes respiration. There is no question that positive pressure therapy is an option only for patients whose optimum dosage has been established and whose pharmacological treatment has been stabilized. On a case-by-case basis, oxygen therapy may be prescribed for mild forms of Cheyne-Stokes respiration. It should be noted that this type of therapy – compared to current and more effective types of treatment – is clearly regressive. In addition to pharmacological treatment, the following therapy options are available (11, 44):

- Oxygen inhalation
- CPAP
- Bilevel
- Anticyclical modulated ventilation

Oxygen inhalation

Supplemental oxygen provided during the night increases oxygen concentration and arterial CO_2 partial pressure in patients with Cheyne-Stokes respiration (45, 63). This therapy increases oxygen and carbon dioxide stores and consequently suppresses the drive of peripheral chemoreceptors. Respiratory regulation is checked and the CO_2 response reduced. Studies have proven that supplemental oxygen can reduce the AHI, arousal index and the extent of oxygen desaturation (45). In addition, a slight reduction in central apnea and hypopnea has been recorded with use of intranasal oxygen delivery (46). It has furthermore been shown that hypercapnic ventilatory response (HCVR) is reduced by nighttime inhalation of oxygen (47) along with a significant reduction in AHI and the nighttime level of norepinephrine in urine (39). The individual studies sound promising at first, but results of other studies contradict them, claiming no improvement in sleep architecture was achieved and a reduction of only 50 % in Cheyne-Stokes respiration was seen (39, 62). In summary, these results are not sufficient reason to recommend oxygen inhalation in general for this patient group. This therapy may be used only in mild cases and for patients who reject mask ventilation or for whom mask therapy is not suitable.

Oxygen inhalation combined with dosage of CO_2

Cheyne-Stokes respiration can be effectively reduced when CO_2 is delivered along with oxygen (38). Moreover, improved arterial oxygen saturation and a rise in transcutaneous CO_2 can be achieved. At the same time, however, increased sympathetic nerve activity is induced. This effect leads to the conclusion that the combined inhalation of O_2 and CO_2 should not be used for CSR patients.

CPAP

As in the past, CPAP therapy is the standard choice for patients with obstructive sleep apnea. Studies have been made of the use of CPAP therapy on patients with manifest heart failure and Cheyne-Stokes respiration. Early results show that the use of CPAP therapy brings about a significant reduction in AHI, an increase in oxygen saturation and an improvement in sleep structure (48). One study proved that CPAP significantly increased left ventricular ejection fraction (LVEF) as compared to a control group (49). In a clinical trial with a five-year follow-up, patients under CPAP showed a relative risk reduction in the combined mortality-cardiac transplantation rate (8). Unfortunately, these results could not be confirmed by the prospective, randomized and extensive CANPAP study (50, 51) although a sub-group of study patients did benefit from CPAP therapy. The lack of success in the prematurely terminated study was attributed to methodological weaknesses. The CPAP therapy with the study's targeted pressure of 10 mbar did not completely suppress apnea. Furthermore, changes in the drug treatment of heart failure (introduction of beta blocker therapy, discontinuation of digitalis therapy) made during the study yielded a reduction in patient mortality and need for transplantation, so that the previously calculated event prediction (death, heart transplant) did not correspond to reality. Furthermore, the study pointed to a possible worsening of cardiac function prompted by CPAP-induced pre-load decrease in some heart failure patients. The results led to the conclusion that CPAP therapy would no longer be recommended as an option for patients with Cheyne-Stokes respiration.

Bilevel therapy

Even less data are available on the use of bilevel than on CPAP therapy for treatment of heart failure and Cheyne-Stokes respiration. One study was able to show that bilevel therapy reduced Cheyne-Stokes respiration and improved sleep structure. A reduction in AHI, a decrease in the arousal index and improvement in cardiac function were also documented (52). The therapeutic effectiveness, however, does not appear to be convincing. Considering the fact that bilevel therapy was originally developed for treatment of hypercapnic respiratory insufficiency, it seems that the treatment with balanced hyperventilation and consecutive hypocapnia is rather "counterproductive".

CS therapy with ACMV

Anticyclical Modulated Ventilation (ACMV), also referred to as adaptive servo-ventilation (ASV) in the literature, is another approach in the treatment of patients with severe heart failure and Cheyne-Stokes respiration. Because patients generally hyperventilate, in classic ASV the therapeutic approach is to dampen respiration, which is de facto anticyclical ventilation. In effect, ASV provides more respiratory support when the patient's own breathing is marginal and reduces support when the patient's own breathing is greater. The acute effect of ASV on sleep quality and respiration appears to be considerably superior to that of oxygen, CPAP and bilevel (ST) therapy (53, 54).

The ACMV process is enhanced in SOMNO*vent* CR (see Function and algorithm).

With SOMNO*vent* CR a new type of therapy is utilized for patients with central respiratory regulation disorders such as Cheyne-Stokes respiration, possibly accompanied by obstructive sleep-related breathing disorders. In contrast to classic ASV, CR mode does not react to the current ventilation in relation to mean spontaneous breathing, but to changes (differences) in ventilation from one breath to the next. This mode permits physiological variability in spontaneous breathing as it occurs, particularly during waking, the wake-sleep transition and REM sleep as long as breathing remains stable and does not show cyclical fluctuations. The goal is to stabilize breathing in a range close to the long-term mean of spontaneous breathing. A current study shows that anticyclical pressure application is superior to NPPV (non-invasive positive pressure ventilation) also in the treatment of complex sleep apnea (64).

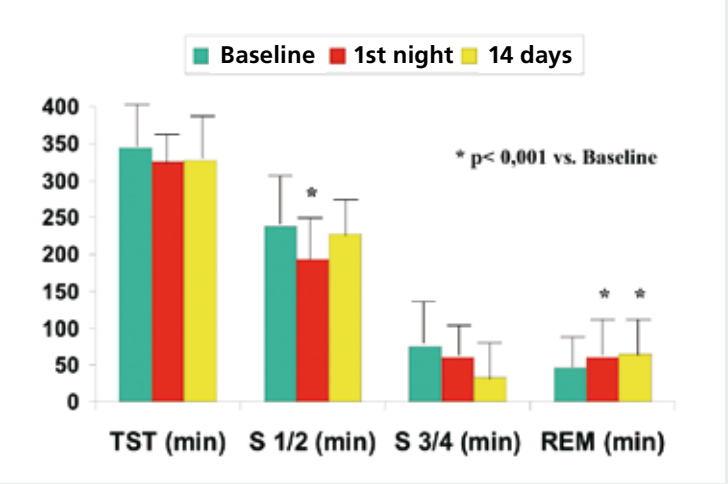
10. Initial study results with SOMNO*vent* CR

The first results from a study conducted with SOMNO*vent* CR were presented at the ERS Congress 2007 in Stockholm (65). The pilot study at Krankenhaus Bethanien in Solingen was subsequently continued and its results presented at DGP 2008 in Lübeck. The background to the study was the fact that patients with Obstructive Sleep Apnea Syndrome (OSAS) who also suffer from Cheyne-Stokes respiration often cannot be effectively treated with CPAP therapy. The goal of the pilot study was to test the therapeutic effectiveness of SOMNO*vent* CR for this patient group.

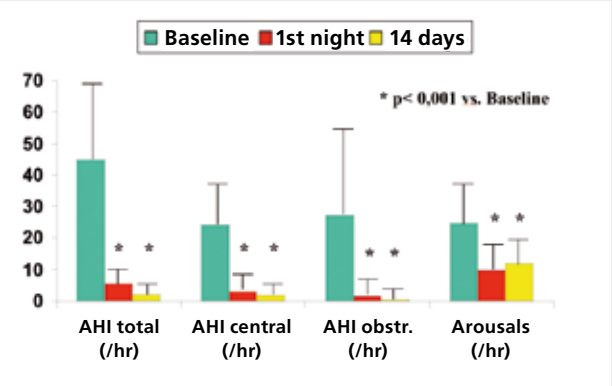
Method:

16 patients (4 women, 12 men; aged 61.2 ± 11.3 years; BMI 31.7 ± 4.4 kg/m²) with recently diagnosed OSAS (< 80 % all events) and CSR (≥ 20 % all events) were admitted to the study. After a diagnostic polysomnogram was made, the device SOMNO*vent* CR was used. Another polysomnogram was made after 14 days.

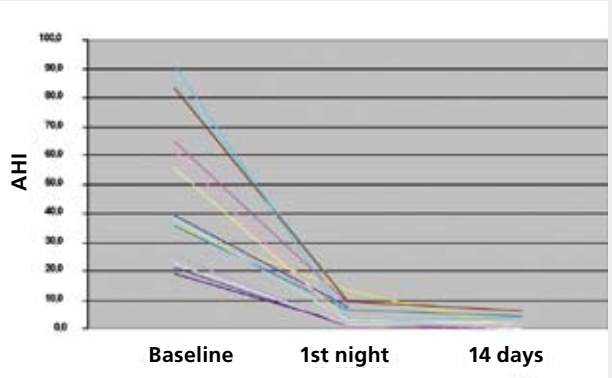
Results:



Ill. 10 Comparison of sleep profile at diagnosis and under SOMNO*vent* CR



Ill. 11
Comparison AHI and arousals during diagnostic night and under SOMNO*vent* CR



Ill.12
Individual cases of AHI during diagnostic night and under SOMNO*vent* CR.
An effective reduction in AHI is possible under SOMNO*vent* CR.

EPAP	**5.7 ± 1.0**	**(range 4.0 – 9.4)**	**cmH_2O**
EEPAP	**8.1 ± 1.1**	**(range 5.6 – 10.6)**	**cmH_2O**
EEPAP	**9.5 ± 1.3**	**(range 5.7 – 16.8)**	**cmH_2O**

Ill.13
Mean applied pressure under SOMNO*vent* CR

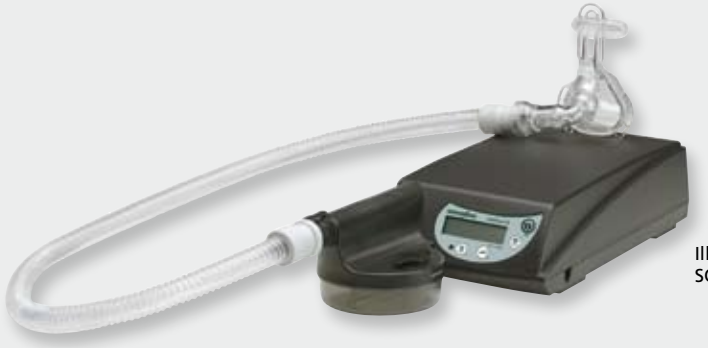
Summary

The new algorithm constitutes effective treatment of patients with a combination of obstructive sleep apnea syndrome (OSAS) and Cheyne-Stokes respiration. After a brief period of treatment, it appears that a further reduction, particularly in central respiratory disorders, is achieved.

NOTE: Illustrations 11-13 courtesy of Krankenhaus Bethanien Solingen/Prof. Randerath

11. SOMNO*vent* CR – Function and algorithm

If therapy is to be successful, central and obstructive events in heart failure patients must be treated. Because this patient group frequently suffers from OSA too and an even larger number of patients indicate mild obstructive events, it is understandable that a therapy device for treatment of Cheyne-Stokes respiration alone cannot adequately detect and treat these respiratory disorders. SOMNO*vent* CR was developed with this challenge in mind.



Ill.14
SOMNO*vent* CR

SOMNO*vent* CR functional principle

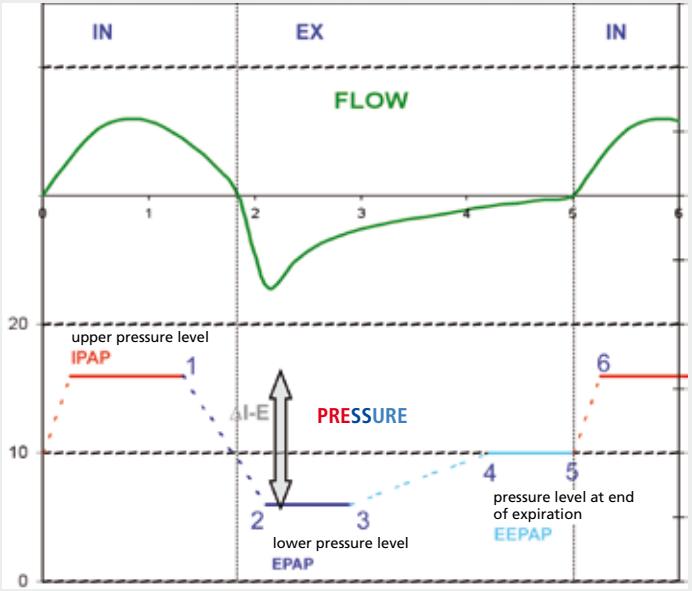
The device has three pressure levels:

1. IPAP = upper pressure level during inspiration
2. EPAP = lower pressure level at start of expiration
3. EEPAP = pressure level at end of expiration

IPAP pressure provides the inspiratory splint and "ventilation"; EPAP pressure makes exhalation easier and ventilation more comfortable for the patient; EEPAP is the minimum level required to eliminate obstructive events. The self-adjusting difference: IPAP to EPAP (delta-I:E) supports breathing through anticyclical modulation. A decrease in EPAP achieves expiratory pressure relief comparable to softPAP.

Depending on the events detected by the device, the three pressure levels – IPAP (upper pressure level during inspiration), EPAP (lower pressure level at start of expiration) and EEPAP (pressure level at end of expiration) – automatically adjust to the current needs of the patient (cf. Ill. 15).

SOMNO*vent* CR functional priniciple



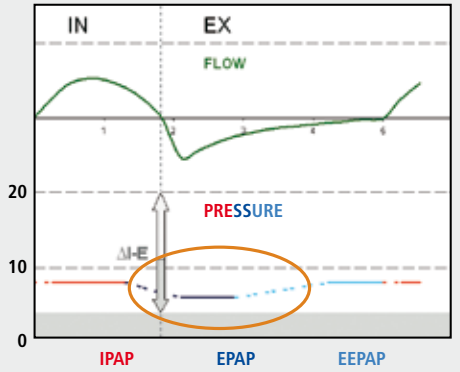
Ill. 15
The three pressure levels and what they mean

Pressure level

Point 1:	**Start of decrease:**	Inspiration maximum is safely past
Point 2:	**End of decrease:**	Pressure decrease depends on respiratory rate, max. rise and timing are determined by turbine idling cycle
Point 3:	**Start of increase:**	Expiration maximum is safely past
Point 4:	**End of increase:**	Pressure increase depends on respiratory rate
Point 5:	**Start of inspiration:**	Switch to IPAP (when IPAP > EEPAP) – and if point 4 has not yet been reached
Point 6:	**IPAP or EEPAP has been reached**	

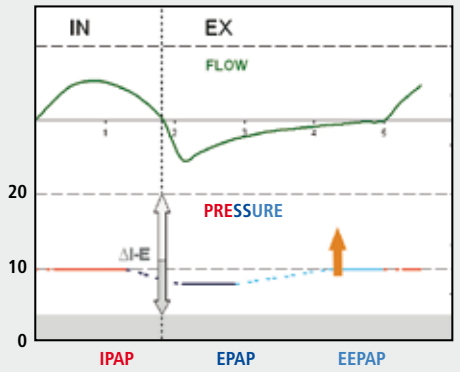
The three different pressure levels effectively treat both periodic Cheyne-Stokes respiration and co-prevalent obstructive sleep apnea syndrome.

Normal respiration



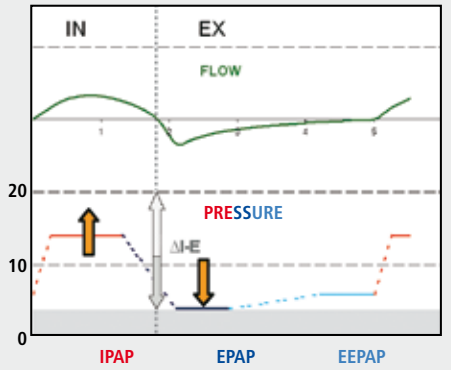
Ill. 16
Normal respiration
The situation is shown during normal respiration when the device applies pressure relief (softPAP) (EPAP pressure). Prior to the transition to expiration, the therapy pressure is reduced to make exhalation easier and to increase patient comfort. Well in advance of the end of expiration, the pressure is again raised to EEPAP.

Obstructions



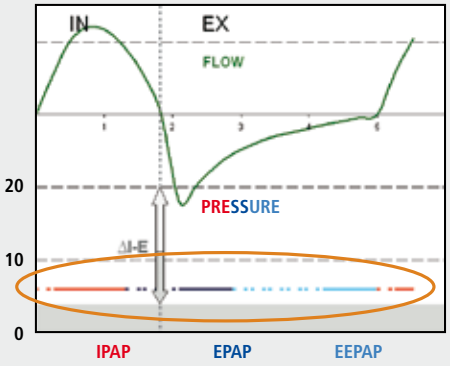
Ill. 17
Obstructive Event
Upon detection of obstructions (epochs with apnea, hypopnea, flow limitations or snoring), EEPAP is raised in order to hold airways open. This is an auto-CPAP function (auto-EEPAP), which adjusts to current needs.

Hypoventilation and apnea



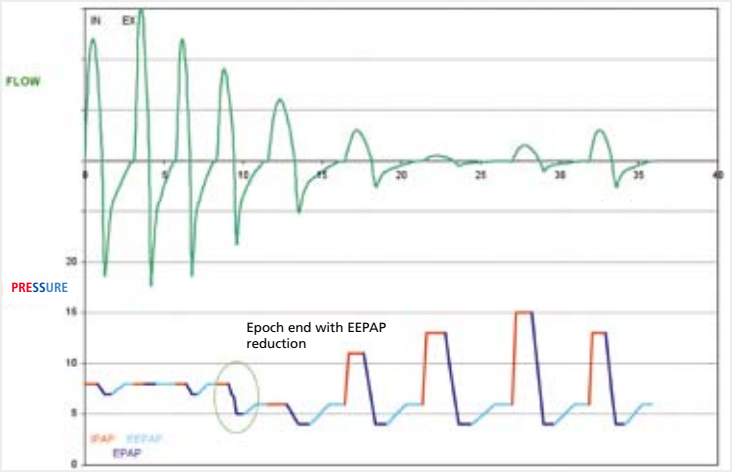
Ill. 18
Decreasing respiratory minute volume and apnea
As respiratory minute volume (RMV) decreases, the device supports patient's breathing with a continuous increase in the IPAP/EPAP difference (grey arrows). In the event of apnea (breathing stops), the device automatically ventilates the patient at a patient-specific rate (similar to ST mode).

Hyperventilation



Ill. 19
Increasing respiratory minute volume (hyperventilation)
As RMV increases, the IPAP/EPAP-difference is reduced to zero (compare CPAP) in order to stabilize breathing (see colored lines at the same level).

Dynamic reaction of three pressure levels



Ill. 20
Dynamic reaction of pressure levels with reduction of EEPAP at end of epoch
The illustration shows the device's dynamic reaction to changes in flow. In the first phase the device reduces the IPAP/EPAP difference to zero in response to hyperventilation. Furthermore, EEPAP pressure is reduced (see circle) at the end of an epoch in response to a prolonged period of obstruction-free breathing. The patient now develops hypopnea or apnea. On the basis of central events, the device-delivered breath (IPAP-EPAP difference) is increased breath for breath until the moment the patient flow resumes. Apparent in reduced breath.

Device operation

Device settings

Physician menu

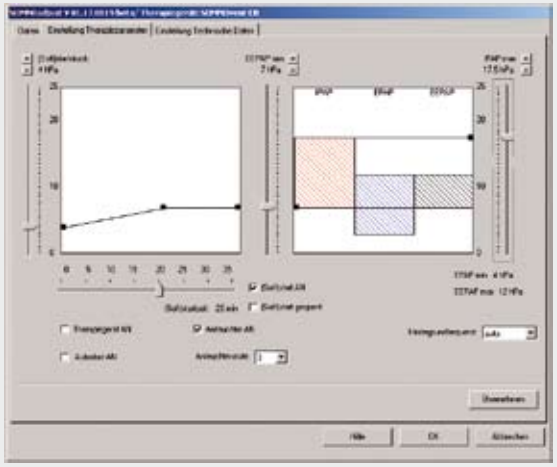
Parameter	Display	Range
Lower EEPAP limit	P_{min} EEPAP	6 hPa to 12 hPa
Upper IPAP limit	P_{max} IPAP	(set lower EEPAP limit + 5 hPa) to 20 hPa
Backup rate	bF	8 Auto
Autostart	Auto	on OFF
Softstart pressure	P	4 hPa to lower EEPAP limit
Softstart time	min	5 to 30 minutes
Humidification level		1 to 6
Time		hr/min
Date		T/M/J
Clear date	cLEAr dAtA	

Patient menu

Parameter	Display	Range
Length of therapy	h	
Autostart	Auto	on OFF
Softstart time	min	5 to 30 minutes
Humidification level		1 to 6
Drying mode	dr 0:30	
Filter change		

Ill. 21
Parameter setting

Setting via software



Ill. 22
Parameter setting via software:
The illustration shows the layout of settings for pressure limits. Note that the upper limit for IPAP must be at least 5 hPa above the lower EEPAP limit. The setting makes clear the dependence of the pressures on each other.

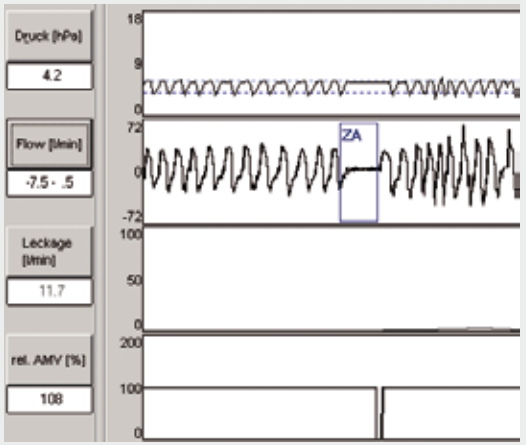
Device setting recommendations

Patient Type	Setting			Expected response
	EEPAPmin	IPAPmax	Other	
Pre-setting	6 hPa	16 hPa	Automatic backup rate	
Periodic / CSR or central sleep apnea without obstructive elements combined with low EF or pulmonary edema	Increase gradually from 6 to 10 hPa; stop increasing if pressure induces central events or glottic closure	EEPAPmin + 6-7 hPa; continue increase if IPAP max is frequently reached or obstructions are detected. Note: Not in cases of glottic closure reflex	Use Softstart with full face mask first, check leakage development in software; reduce IPAPmax and EEPAPmin at least initially in cases of: - glottic closure reflex - pressure-induced central events - lack of pressure tolerance	No apnea, hypopnea during first nights of therapy; monitor again later
Same as above but without low EF or pulmonary edema	6 hPa	12-14 hPa, see text above		
Periodic / CSR or central sleep apnea with obstructive elements	Appropriate to indication ≥ 6 hPa, as long as no central events or glottic closure are induced	16 -18 hPa; if IPAPmax is frequently reached and reaction to central events remains inadequate, increase pressure		
Complex sleep apnea	6 hPa up to titrated CPAP	16-18 hPa, if IPAPmax is frequently reached and reaction to central events remains inadequate, increase pressure	Use Softstart, to make falling asleep easier	No apnea; in case of residual obstructions > Bilevel ST
One of the above indications with generally lower oxygenation (respiratory insufficiency)	Appropriate to indication	Appropriate to indication	Additional oxygen as required	No apnea; if pressure level is inadequate > Bilevel ST
One of the above indications with greatly varied respiratory rate	Appropriate to indication	Appropriate to indication	Backup respiratory rate as required	No apnea; if pressure level is inadequate > Bilevel ST

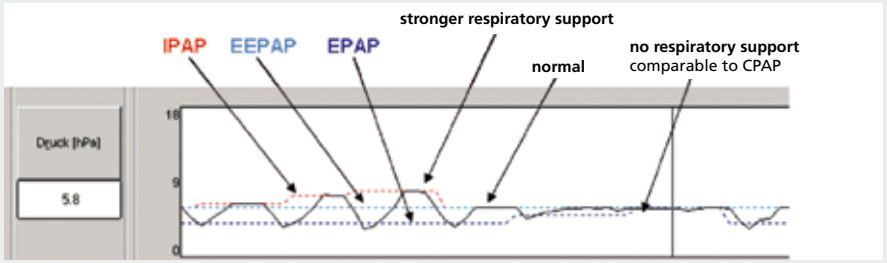
SOMNO*vent* CR regulation

Initialization phase

The initialization phase lasts a few minutes. Its purpose is to determine the normal minute volume. The first part of the initialization phase is "discarded" so that the effects of patient acclimation to the mask and ventilation, which usually gives rise to mild hyperventilation, are not taken into consideration. As during normal respiration, the device reduces pressure to EPAP. During the initialization phase there is no reaction to events.



Ill. 23
Initialization phase
No regulation is made during the initialization phase. Central apnea is shown here.



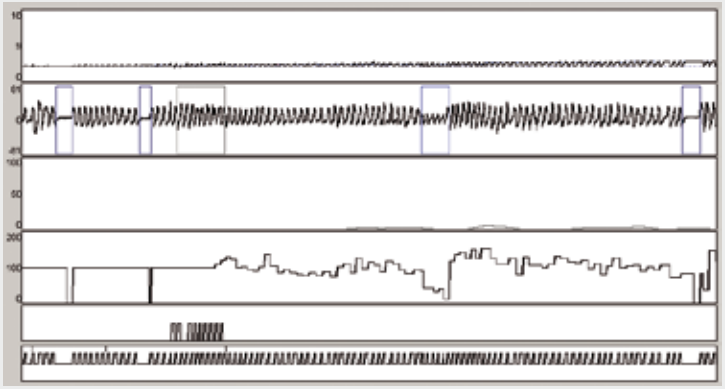
Ill. 24
Internal regulation of three pressure levels
This example shows the pressure curve at three levels (IPAP, EPAP, EEPAP) during hypoventilation, normal respiration and hyperventilation.

SOMNO*vent* CR regulation

Type	Identifying characteristics	Sample flow signal	Reaction
Normal respiration	Relative RMV is stable		ΔI-E = 2 hPa
Decreasing respiratory minute volume (RMV)	Breathing present, relative RMV falls		ΔI-E is increased (until EPAPmin and IPAPmax are reached
Apnea	Breathing stops (longer than a timeout), with time-cycled (mandatory) ventilation, flow can be generated by device		Time-cycled, mandatory breath (ST mode) is successively increased in cases of inadequate (too low) respiratory volume
Increasing respiratory minute volume	Breathing present, relative RMV climbs		ΔI-E is reduced (until CPAP is reached)

Ill. 25
The table shows the regulating reaction to various central respiratory events and in comparison to normal respiration and to increasing respiratory minute volume. Decreasing respiratory minute volume is answered with an anticyclical breath while the response to apnea is a mandatory breath.

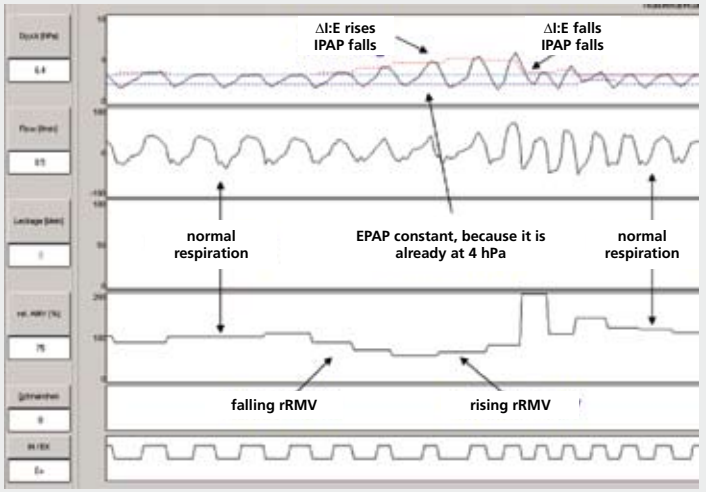
Softstart



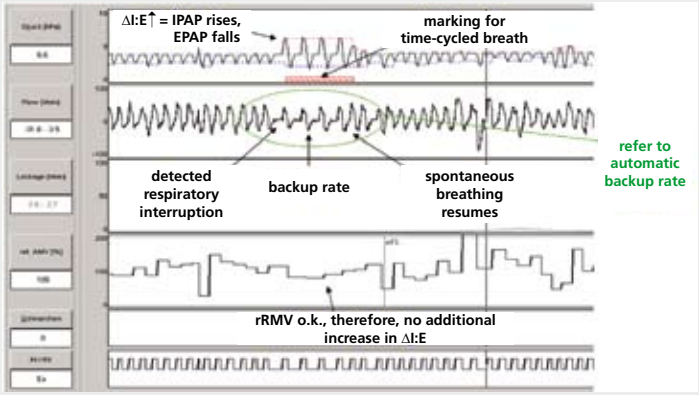
Ill. 26
During Softstart the EEPAP is raised continuously from the pre-set Softstart pressure (initial setting = 4 hPa) to EEPAPmin. There is no reaction to events. As during normal respiration, the pressure is lowered to EPAP, but never to a level below 4 hPa. At the end of Softstart, there is a shortened initialization phase since the patient has already become accustomed to the mask and ventilation.

Practical examples

Examples of regulation
Central respiratory event and decreasing respiratory minute volume

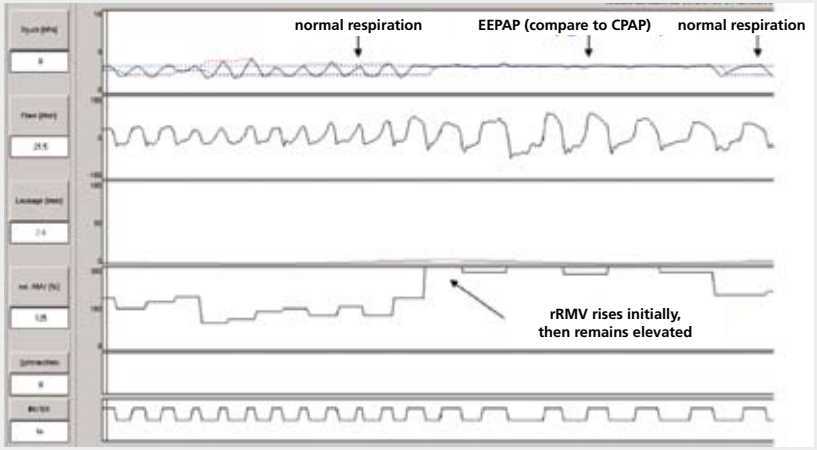


Ill. 27
Practical example
Central respiratory event with decreasing respiratory minute volume
The response to a decrease in relative respiratory minute volume is anticyclical modulation of ΔI:E, as needed.



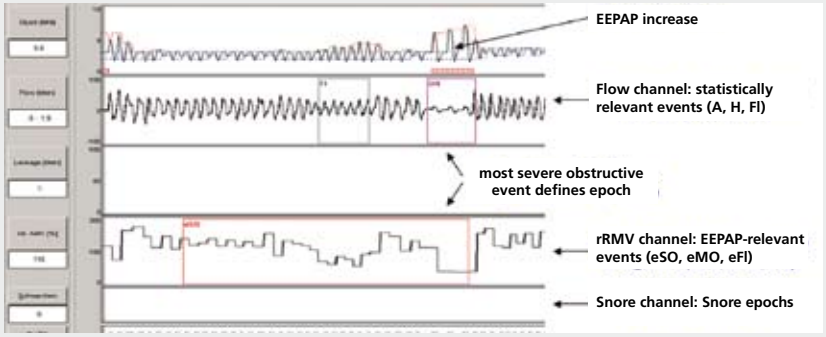
Ill. 28
Practical example
Central respiratory event with apnea
Mandatory breaths are initiated by apnea (ST mode); when respiratory minute volume does not reach a sufficient level, an increase is made in ΔI:E.
When normal respiration is resumed, ΔI:E is reduced.

Central respiratory event with increasing respiratory minute volume



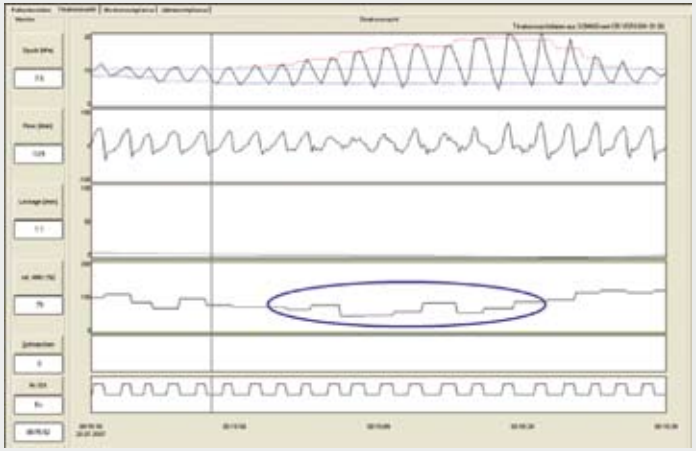
Ill. 29
Practical example
Central respiratory event with increasing respiratory minute volume
In response to increasing respiratory minute volume, ΔI:E is reduced to a pressure level equal to EEPAP (comparable to CPAP). When normal respiration resumes, the pressure is increased to 2 hPa in that the IPAP corresponds to EEPAP pressure and the EPAP is reduced by 2 hPa.

Obstructive respiratory events — epoch principle



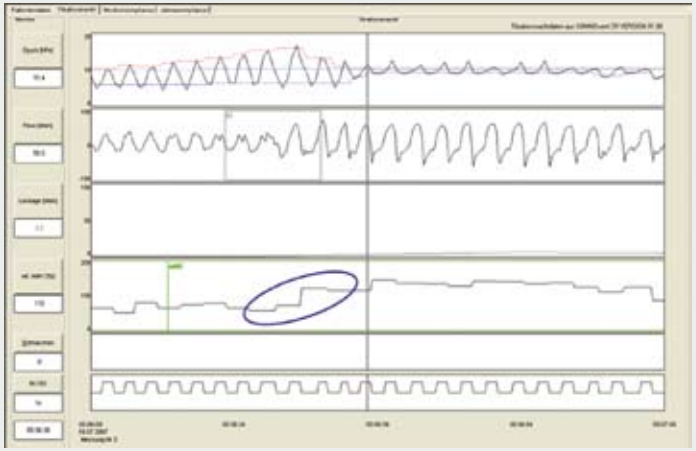
Ill. 30
Practical example
Regulation of obstructive event: epoch principle
Events are observed during a two-minute epoch and analyzed. A pressure reaction in the form of a change to EEPAP takes place at the end of the epoch. Exception: If an obstruction is detected during time-cycled breaths, EEPAP is increased immediately. The decisive factor is the most severe obstructive event within an epoch. The epochs are marked in the rel. RMV channel with regard to their most severe obstructive events. If no obstructive event is detected within an epoch, the EEPAP is decreased at the end of the epoch after the event-related and pressure-dependent waiting period has expired.

Obstructive event – mild obstruction



Ill. 31
Practical example
Mild obstruction due to respiratory deficit and flattening
Here the reduction in relative RMV is not sufficient to induce hypopnea, but it can lead to desaturation because it accumulates over several breaths. Therefore, this is a relevant event with pressure reaction.

Obstructive event – mild obstruction with troubled breathing



Ill. 32
Practical example
Mild obstruction as a result of flattening and troubled breathing
Also an example of reduced rRMV which does not correspond sufficently to criteria for hypopnea, but the sudden volume increase at the end of flattening indicates an arousal (respiratory effort-related arousal or RERAS). Therefore, it is a relevant event.

Summary of regulation

SOMNO*vent* CR reacts as follows

- In case of decreasing respiratory minute volume SOMNO*vent* CR supports breathing by increasing the IPAP/EPAP difference.
- When apnea occurs, the device automatically ventilates at a rate adapted to the patient (like ST mode).
- In case of increasing respiratory minute volume, the IPAP/EPAP difference is reduced down to zero (comparable to CPAP) in order to calm down and quiet the patient's breathing.
- If obstructive events occur (epochs with apnea, hypopnea, flow limitation or snoring), EEPAP is raised in order to keep the airway open (= auto EEPAP).
- During normal respiration, pressure relief (softPAP) is applied. Before the transition to expiration, therapy pressure is reduced to make it easier for the patient to exhale. Just before the expiratory phase ends, the pressure is increased to the EEPAP level to prevent the airways from closing during this collapse-prone point in the respiratory cycle.

Compared to therapeutic methods with fixed pressure levels (CPAP, bi-level), anti-cyclical modulated ventilation has considerable advantages:

- It balances out respiratory fluctuations with an anticyclical response and thereby modulates pathophysiological respiration in a physiological direction (suppresses hyperventilation in the process).
- The new CR mode in particular registers central and obstructive patterns and provides therapeutically effective regulation (of Cheyne-Stokes respiration, obstructive events).
- Complex sleep apnea can also be effectively treated.
- ACMV regulates breathing gently and thus guarantees restorative sleep.
- The intelligent algorithm's adjustment to the patient throughout the night leads to ongoing improvement in therapy effectiveness.

Contraindications

Consideration should be given to the following contraindications. It is up to the doctor to decide on a case-by-case basis whether this type of therapy is indicated.

- Severe cardiac decompensation
- Severe cardiac arrhythmia
- Right heart failure or other pulmonary hypertension
- Atrial fibrillation with reduced filling of the right ventricle
- Severe hypertension, especially in connection with intravascular volume depletion
- Severe epistaxis
- High risk of barotrauma
- Respiratory insufficiency with causes other than OSA (e.g., COPD, pulmonary emphysema)
- Severe hypoxemia or hypercapnia during the day
- Nocturnal hypoxemia with origins other than OSA, Cheyne-Stokes breathing (e.g., obesity hypoventilation syndrome)
- Pneumothorax or pneumomediastinum
- Pneumoencephalus
- Cranial trauma
- Status after brain surgery and surgery involving the pituitary gland (hypophysis) or the middle or internal ear
- Acute sinusitis, middle ear infection (otitis media) or eardrum (tympanum) perforation

Side effects

In rare cases the following side effects may occur during therapy:

- Marks left on the face from contact points of nasal or full face masks and in the area around the forehead cushion
- Reddening of facial skin
- Congested nose
- Dry nose and mucous membranes
- A feeling of dry mouth in the morning
- Sinus pressure
- Irritation of conjunctiva
- Gastrointestinal insufflation
- Nosebleed

As a rule, side effects can be effectively prevented with a good fit of the mask and timely humidification of respiratory air.

12. Practical tips

What to consider when making the initial settings

- The first use of the therapy device (positive airway pressure) should take place under medical supervision.
- The patient's pharmacological therapy should have stabilized his condition.
- A current echocardiogram should be available.
- There should be no clinical indications of hypovolemic heart failure.
- Systolic blood pressure should be ≥ 100 mmHg.
- Heart failure patients suffer from dyspnea and fear mask ventilation. A practice session of one to two hours, preferably in the afternoon, is recommended to help patients become accustomed to the therapy. If the patients develop claustrophobia during mask ventilation, it is often helpful to feed supplemental oxygen at a rate of one to two liters per minute. The oxygen reduces the patient's respiratory stimulus. It may also help to treat the patient with a nasal mask during the day and switch to a full face mask at night.
- The time spent on the initial settings is well invested since it normally has a positive effect on compliance.
- Indispensable: Therapy should take place with blood pressure monitoring during the day. Background: Some patients show blood pressure decreases under positive pressure ventilation. If the blood pressure falls by 10 mmHg, titration must be interrupted and an alternative therapy should be considered (cf. blood pressure test). Explanation: RR is an indirect measurement parameter of cardiac ejection fraction. In pharmacological therapy of heart failure, medications are used that reduce afterload (and thereby cause blood pressure to fall). A blood pressure drop can result from the increase in intrathoracic pressure brought on by positive pressure therapy (PAP). It may be possible to use PAP therapy after an adjustment to the pharmacological therapy (e.g., reduction in dosage of diuretics).
- Titration may take several nights.

Special attributes in patient interface and Cheyne-Stokes respiration

Patients with Cheyne-Stokes respiration hyperventilate. All patients breathe through the mouth during C-S respiration phases. Therefore, patients should be given a full face mask at least while they are becoming accustomed to the therapy. Particularly gaunt patients with high cheekbones sometimes have difficulties adjusting to masks, as do patients who wear dentures or who have thin skin.

Ill. 33
JOYCE Full Face – a full face mask with a good fit and very little dead space

If therapy proves effective, it may be possible to switch to a nasal mask later. Such a change is necessary, however, for only about one-fifth of all patients.

Ill. 34
JOYCE – a comfortable and skin-friendly nasal mask

Blood pressure test

To consider when initiating therapy:

Prior to the start of therapy, blood pressure (RR) should be measured under medical supervision. If basal systolic blood pressure is < 100 mmHg, therapy should not be started or in exceptional cases, started only after careful consideration by the doctor. Another RR measurement should take place after five and again after 20 minutes of therapy. When the trial session ends, another RR measurement should be made. Drops in systolic blood pressure (e.g., 10 mmHg) during therapy are generally to be interpreted as a reduction in cardiac output.

In that case therapy should be discontinued. In nervous patients a slight RR decline may cease after therapy begins and the patient calms down.

Therapy should also be discontinued if the patient shows signs of suddenly occurring sleepiness, hearing loss or pallor, or reports feeling faint or cold.

Humidification

Many patients complain of dryness in mucous membranes caused by therapy. The problem is compounded by diuretics, which heart failure patients must take.

Humidification of respiratory air can help to improve comfort and increase patient compliance.

Ill. 35
SOMNO*click* 300

Assessment of therapy quality with SOMNO*vent* CR

Introduction

During therapy with SOMNO*vent* CR the patient should not develop any central or obstructive apnea. However, given the complex pathophysiology of CSR and potentially co-prevalent OSA, an immediate and complete elimination of respiratory disorders cannot be expected. Central apnea is often replaced by hypopnea during therapy. If a relevant AHI remains after the first night of therapy, a distinction should be made between central AI and HI. If central HI is higher than it was before therapy and AI is starkly reduced, the therapy is considered a success. Some patients need several nights of therapy before their breathing patterns normalize.

If apnea occurs despite therapy, a reflective glottis closure could be the reason. Possible causes are:

- pronounced CSR
- low CO_2
- may be prompted by therapy initiation

Under these circumstances it makes sense to use Softstart and to allow the patient a stabilization period of about 60 minutes under therapy.

Follow-up

Compliance

Compliance is influenced by the level of commitment shown during the introductory phase. Time invested now has a positive effect on therapy compliance. An assessment of compliance should consider that the CSR patient, unlike the OSA patient, does not feel the psychological strain of daytime sleepiness. Consequently, the patient frequently perceives no ad hoc improvement from therapy but sees it instead as a disruptive factor (mask ventilation in bed). The first week of therapy is the "critical phase". If the patient "survives" this period, compliance is mostly very good. Some patients need more time for acclimation.

Warning: Poorly fitting masks are the main cause of lack of compliance. Therefore, take more time to explain the mask and to show the patient how to put it on correctly.

Perceptible effect for patient

When no longer disturbed by nighttime paroxysmal dyspnea and nocturia, patients can breathe better and sleep throughout the night. Within a short time they notice an improvement in quality of life.

Tip:

Some patients tolerate only very low pressures during therapy initiation even in the absence of a hemodynamic functional disorder. Under these circumstances patients may need another control night to adapt. Medium to long-term improvements in physical performance can be determined by the six-minute walking test, LVEF as captured in an echocardiogram and a reduction in daytime dyspnea.

Good follow-up demands the presence of medical personnel, especially after the first night of therapy, but also during the first week of therapy at home.

Which patient is right for this therapy?

Increasing numbers of patients with mixed apnea or comorbidity are being seen. The following is an attempt to define those types:

	(Home) Ventilation patients	CSR patients
	A rather rigid breathing pattern	Highly variable spontaneous breathing
	Elevated CO_2	Low to normal CO_2
	Hypercapnic	Hypocapnic
	Ventilation disorder, respiratory insufficiency or respiratory pump fatigue	Hyperventilation (too strong CO_2 response), loss of respiratory stability
Goal	Unload respiratory pump, stabilize/ lower CO_2	Stabilize spontaneous breathing
Therapy	Slight "running over" of normal breathing or controlled ventilation	Anticyclical counteraction of CO_2 fluctuation, damping of unstable system
Compliance	Good, due to perceptible relief	Rather low, due to mask and influence of spontaneous breathing
Backup rate	Should be the same as or higher than spontaneous breathing in order to relieve breathing and keep CO_2 at normal level	Should allow variability in spontaneous breathing and let CO_2 rise beyond hypocapnia level

13. Outlook

The emergence of Cheyne-Stokes respiration in heart failure patients is a poor prognostic sign which demands immediate clarification and treatment. Accompanying obstructive nighttime respiratory disorders should be treated in parallel as they represent an added cardiovascular/ cerebral risk that should not be underestimated.

SOMNO*vent* CR is the therapy of choice for these patients because it effectively treats the central respiratory regulation disorder Cheyne-Stokes respiration and accompanying obstructive sleep apnea. Moreover, it is suitable for treatment of complex sleep apnea.

A number of questions remain unanswered at this time. For example, whether and in what way sleep-related central and obstructive breathing disorders are related and how pathophysiological events look in detail.

In light of the enormous significance of this disease for current-day medicine, expectations are high for new scientific findings which may contribute to improving the condition of affected patients and thus their life expectancy and quality of life.

SOMNO*vent* CR is a step in the right direction.

14. Bibliography

1. Armstrong P.W., Moe G.W.: Medical advances in the treatment of congestive heart failure, Circulation 88: 2941-2952 (1993)
2. Hanly P.J. et al.: Respiration and abnormal sleep in patients with congestive heart failure. Chest 96: 480-488 (1989)
3. Javaheri S. et al.: Sleep apnea in 81 ambulatory male patients with stable heart failure. Circulation 97: 2154-2159 (1998)
4. Javaheri S. et al.: Occult sleep-disordered breathing in stable congestive heart failure. Ann Inter Med 122: 487-492 (1995)
5. Wieber St.J.: The cardiac consequences of the obstructive sleep apnea-hypopnea syndrome. The Mount Sinai Journal of Medicine 72 (1): 10-12 (2005)
6. Report of the American Academy of Sleep Medicine Task Force: Sleep-related breathing disorders in adults: recommendations for syndrome definition and measurement techniques in clinical research. Sleep 22 (5): 667-689 (1999) .
7. Lanchfranchi P.A. et al.: Prognostic value of nocturnal Cheyne-Stokes respiration in chronic heart failure. Circulation 99: 1435-1440 (1999)
8. Sin D.D., et al.: Effects of continuous positive airway pressure on cardiovascular outcomes in heart failure patients with and without Cheyne-Stokes respiration. Circulation 102: 61-66 (2000)
9. Cheyne J.: A case of apoplexy in which the flesh part of the heart is turned to fat. Dublin Hospital Report 2: 216-223 (1818)
10. Stokes W.: The disease of the heart and the aorta. Hodeges and Smith, Dublin: 323-326 (1854)
11. Virchow et al.: Schlafmedizin. Dustri-Verlag Dr. Karl Feistle (2004)
12. Yang F., Khoo M.C.: Ventilatory response to randomly modulated hypercapnia and hypoxia in humans. J Appl Physiology 76 (5): 2216-2223 (1994)
13. Solin P. et al.: Peripheral and central ventilatory responses in central sleep apnea with and without congestive heart failure. Am J Respir Crit Care Med 162 (6): 2194-2120 (2000)
14. Badr M.S. et al.: Treatment of refractory sleep apnea with supplemental carbon dioxide. Am J Respir Crit Care Med 150 (2): 561-564 (1994)
15. Zhou et al.: Effect of testosterone on the apneic threshold in women during NREM sleep. J Appl Physiolol 94 (1): 101-107 (2003)
16. Zhou et al.: Effect of gender on the development of hypocapnic apnea/hypopnea during NREM sleep. J Appl Physiol 89 (1):192-199 (2000)
17. Gothe et al.: Effect of quiet sleep on resting and CO_2–stimulated breathing in humans. J Appl Physiol 50(4): 724-730 (1981)
18. Rist K.E. et al.: Effect on non-REM sleep upon respiratory drive and the respiratory pump in humans. Respir Physiol 63 (2): 241-256 (1986)

19. Douglas N.J. et al.: Respiration during sleep in normal man. Thorax 37 (11): 840-844 (1982)
20. Douglas N.J. et al.: Hypercapnic ventilatory response in sleeping adults. Am Rev Respir Dis 126 (5): 758-762 (1982)
21. Phillipson E.A. et al.: Control of breathing during sleep. Am Rev Respir Dis 118 (5): 909-939 (1978)
22. Bradley T.D. et al.: Clinical and physiologic heterogeneity of the central sleep apnea syndrome. Am Rev Respir Dis 134 (2): 217-221 (1986)
23. Xie A. et al.: Hypocapnia and increased ventilatory responsiveness in patients with idiopathic central sleep apnea. Am J Respir Crit Care Med 152 (6Pt1): 1950-1955 (1995)
24. Van de Borne P. et al.: Effect of Cheyne-Stokes respiration on muscle sympathetic nerve activity in severe congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. Am J Cardiol 81(4): 432-436 (1998)
25. Hedner J. et al.: Reduction in sympathetic activity after long-term CPAP treatment in sleep apnea: cardiovascular implications. Eur Respir J 8 (2): 222-229 (1995)
26. Guyton A.C.: Basic oscillating mechanism of Cheyne-Stokes breathing. Am J Physiol 187: 395-398 (1956).
27. Naughton M. et al: Role of hyperventilation in the pathogenesis of central sleep apneas in patients with congestive heart failure. Am Rev Respir Dis 148 (2): 330-338 (1993)
28. Javaheri S., Corbett W.S.: Association of low $PaCO_2$ with central sleep apnea and ventricular arrhythmias in ambulatory patients with stable heart failure. Ann Int Med 128 (3): 204-207 (1998)
29. Hanly P. et al.: Pathogenesis of Cheyne-Stokes respiration in patients with congestive heart failure. Relationship to arterial PCO_2. Chest 104 (4): 1079-1084
30. Xie A. et al. : Apnea-hypopnea threshold for CO_2 in patients with congestive heart failure. Am. J Respir Crit Care Med 165 (9):1245-1250 (2002)
31. Javaheri S.: A mechanism of central sleep apnea in patients with heart failure. N Engl J Med 341 (13): 949-954 (1999)
32. Wilcox I.: Ventilatory control in patients with sleep apnea and left ventricular dysfunction: comparison of obstructive and central sleep apnea. Eur Respir J: 11 (1). 7-13 (1998)
33. Solin P. et al.: Influence of pulmonary capillary wedge pressure on central apnea in heart failure. Circulation: 99 (12): 1574-1579 (1999)
34. Lorenzo-Filho G. et al.: Relationship of carbon dioxide tension in arterial blood to pulmonal wegde pressure in heart failure. Eur Respir J 19 (1): 37-40 (2002)
35. Yu J. et al.: Stimulation of breathing by activation of pulmonary peripheral afferents in rabbits. J Appl Physiol 85 (4):1485-1492 (1982)

36. Sin D.D. et al.: Risk factors for central and obstructive sleep apnea in 450 men and women with congestive heart failure. Am J Respir Crit Care Med: 160 (4): 1101-1106 (1999).
37. Berssenbrugge A. et al.: Mechanism of hypoxia induced periodic breathing during sleep in humans. J Physiol 343: 507-526 (1983)
38. Andreas S. et al.: Treatment of Cheyne-Stokes respiration with nasal oxygen and carbon dioxide. Eur Resp J 12 (2): 414-419 (1998)
39. Staniforth A. D. et al.: Effect of oxygen on sleep quality, cognitive function and sympathetic activity in patients with chronic heart failure and Cheyne-Stokes respiration. Eur Heart J 19 (6): 922-928 (1998)
40. Andreas S. et al.: Nasal oxygen effects on arterial carbon dioxide pressure and heart rate in chronic heart failure. Am J Cardiol 83 (5): 795-798, A10 (1999)
41. Javaheri S. et al.: Effects of nasal O_2 on sleep-related disordered breathing in ambulatory patients with stable heart failure. Sleep 22 (8): 1101-1106 (1999)
42. Mortara A. et al.: Abnormal awake respiratory patterns are common in chronic heart failure and may prevent evaluation of autonomic tone by measures of heart rate variability. Circulation 96 (1): 246-252 (1997)
43. Hanly P. et al: Daytime sleepiness in patients with congestive heart failure and Cheyne-Stokes respiration. Chest 107 (4): 952-958 (1995)
44. Duchna H.-W. et al.: Sleep-disordered breathing and cardio- and cerebrovascular diseases: 2003. Update of clinical significance and future perspectives. Somnologie 7: 101-121 (2003)
45. Hanly P.A. et al.: The effect of oxygen on respiration and sleep in patients with congestive heart failure. Ann Intern Med 111(10): 777-782 (1989).
46. Andreas S. et al.: Cheyne-Stokes respiration and prognosis in congestive heart failure. Am J Cardiol 78: 1260-1264 (1996)
47. Andreas S. et al.: Nocturnal oxygen and hypercapnic ventilatory response in patients with congestive heart failure. Respir Med 92(3): 426-431 (1998)
48. Naughton et al.: Effect of continuous positive airway pressure on central sleep apnea and nocturnal PCO_2 in heart failure. Am J Respir Crit Care Med. 150: 1598-1604 (1994)
49. Naughton et al.: Treatment of congestive heart failure and Cheyne-Stokes respiration during sleep by continuous positive airway pressure. Am. J Respir Crit Care Med. 151(1): 92-97 (1995)
50. Bradley D.T. et al.: Rationale and design of the Canadian continuous positive airway pressure trial for congestive heart failure patients with central sleep apnea-CANPAP. Can J Cardiol 17: 677-684 (2001)
51. Bradley T.D. et al.: Continuous positive airway pressure for central sleep apnea and heart failure. N. Engl. J. Med. 353 (19): 2025-33 (2005)

52. Willson G.N. et al.: Noninvasive pressure preset ventilation for the treatment of Cheyne-Stokes respiration during sleep. Eur Respir J 17 (6): 1250-1257 (2001)
53. Teschler H. et al.: Adaptive pressure support servo-ventilation: a novel treatment for Cheyne-Stokes respiration in heart failure. Am J Respir Crit Care Med. 164 (4): 614-619 (2001)
54. Philippe, C et al., Compliance with and effectiveness of adaptive servoventilation versus continuous positive airway pressure in the treatment of Cheyne-Stokes respiration in heart failure over a six-month period, Heart 92:337-342 (2006)
55. The International Classification of Sleep Disorders, American Academy of Sleep Medicine (2005)
56. Young, T. et al.: Epidemiology of obstructive sleep apnea. A population health perspective. Am.J. Respir Crit Care Med 165 (9): 1217-1239
57. Guilleminault C. et al.: The sleep apnea syndromes. Annu Rev Med 27: 465-484 (1976)
58. Young, T. et al.: The occurence of sleep-disordered breathing among middle-aged adults. N Engl J Med 328: 1230-1235 (1993)
59. Marin, J.M. et al.: Long-term cardiovascular outcomes in men with obstructive sleep apnoea-hypopnoea with or without treatment with continuous positive airway pressure: an observational study, Lancet 365: 1046-1053 (2005).
60. Carlson JT et al.: Augmented resting sympathetic activity in awake patients with sleep apnea, Chest: 103: 1763-168 (1993)
61. IP, MS et al.: Circulating nitric oxide is suppressed in obstructive sleep apnea and is reversed by nasal continuous positive airway pressure, AJCCM, 162: 2166-2171 (2000)
62. Franklin KA, et al.: Reversal of central sleep apnea with oxygen. Chest 111: 163-169 (1997)
63. Teschler, H. et al.: The effect of oxygen on respiration and sleep in patients with congestive heart failure. Ann. Intern. Med. 11: 777-782 (1989)
64. Morgenthaler, T.I et al.: Adaptive servoventilation versus non-invasive positive pressure ventilation for central, mixed, and complex sleep apnea syndrome, Sleep 30: 468- 475 (2007)
65. Galetke et al.: Evaluation of a new algorithm for patients with Cheyne-Stokes breathing and obstructive sleep apnea, Abstract ERS, Stockholm 2007
66. Morgenthaler, T.I. et al.: Complex sleep apnea syndrome: Is it a unique clinical syndrome? Sleep 29: 1203-1209 (2006)
67. Pusalavidyasagar S.S. et al.: Treatment of complex apnea syndrome: A retrospective comparative review, Sleep Medicine 7: 474-479 (2006)
68. Schulz, R. et al.: Sleep apnea in heart failure, Eur Respir J 29: 1201-1205 (2007)

15. Glossary

ACMV = anticyclical modulated ventilation

ASV = adaptive servo-ventilation

CPAP = continuous positive airway pressure

CSR = Cheyne-Stokes respiration

EEPAP = end expiratory positive airway pressure

EPAP = expiratory positive airway pressure

ESS = Epworth sleepiness scale

IPAP = inspiratory positive airway pressure

ITGV = intra thoracic gas volume

NPPV = non-invasive positive pressure ventilation

NYHA = New York Health Association

OSA = obstructive sleep apnea

PCWP = pulmonary capillary wedge pressure

PND = paroxysmal nocturnal dyspnea

Raw = airway resistance

RERA = respiratory effort related arousal

RMV = respiratory minute volume

rRMV = relative respiratory minute volume

RV = residual volume

SOMNO*vent* CR = SOMNO*vent* cardio respiratory

TLC = total lung capacity